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Anabolic Steroids Reduce Muscle Damage Caused by Rotator Cuff Tendon Release in an Experimental Study in Rabbits

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Background: Muscles of the rotator cuff undergo retraction, atrophy, and fatty infiltration after a chronic tear, and a rabbit model has been used to investigate these changes. The purpose of this study was to test the hypothesis that the administration of anabolic steroids can diminish these muscular changes following experimental supraspinatus tendon release in the rabbit.

Methods: The supraspinatus tendon was released in twenty New Zealand White rabbits. Musculotendinous retraction was monitored over a period of six weeks. The seven animals in group I had no additional intervention, the six animals in group II had local and systemic administration of nandrolone decanoate, and the seven animals in group III had systemic administration of nandrolone decanoate during the six weeks. Two animals (group III) developed a postoperative infection and were excluded from the analysis. At the time that the animals were killed, in vivo muscle performance as well as imaging and histological muscle changes were investigated.

Results: The mean supraspinatus retraction was higher in group I (1.8 cm; 95% confidence interval: 1.64, 2.02 cm) than in group II (1.5 cm; 95% confidence interval: 1.29, 1.81 cm) or III (1.2 cm; 95% confidence interval: 0.86, 1.54 cm). Histologically, no fatty infiltration was measured in either treated group II (mean, 2.2%; range, 0% to 8%) or III (mean, 1%; range, 0% to 3.4%), but it was measured in the untreated group I (mean, 5.9%; range, 0% to 14.1%; $p = 0.031$). The radiographic cross-sectional area indicating atrophy and the work of the respective muscle during one standardized contraction with supramaximal stimulation decreased in all groups, but the work of the muscle was ultimately highest in group III.

Conclusions: To our knowledge, this is the first documentation of partial prevention of important muscle alterations after retraction of the supraspinatus musculotendinous unit caused by tendon disruption. Nandrolone decanoate administration in the phase after tendon release prevented fatty infiltration of the supraspinatus muscle and reduced functional muscle impairment caused by myotendinous retraction in this rabbit rotator cuff model, but two of seven rabbits that received the drug developed infections.

Clinical Relevance: This study provides a novel approach that may have potential to diminish the irreparable structural and functional changes of the musculotendinous unit associated with chronic rotator cuff tear, but complications of anabolic steroid use also need to be considered.

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A commentary by Vincent M. Wang, PhD, is linked to the online version of this article at jbjs.org.

After a rotator cuff tendon tear, the musculotendinous unit retracts and the muscle undergoes atrophy, fatty infiltration, and fibrosis with loss of contractility and elasticity[1-5]. The torn tendon undergoes atrophy and structural disorganization[6]. A tendon-to-bone repair becomes increasingly difficult because of increased passive tension within the shortened musculotendinous unit and the poor tendon quality[2]. If a repair is technically feasible, healing is uncertain[7-9]. To date, full anatomical and functional restoration of a deteriorated musculotendinous unit has not been achieved. Continuous relengthening experimentally restored architectural changes caused by chronic rotator cuff tearing in a sheep model[10]; fibrosis and atrophy of the muscle were halted and partially reversed by continuous traction and staged repair, but fatty infiltration could not be reversed either experimentally or clinically. New strategies for the prevention, or at least the reduction, of muscle degeneration are of substantial interest.

A patient may not always be aware of the onset of a rotator cuff tear. Even if such an event is known, surgery may not always be clinically necessary or practical. Prevention of muscle degeneration, however, always appears desirable to allow further treatment options to be successful. Pharmacologic prevention of muscle changes incurred by chronic retraction has not been investigated, as far as we know. There are substances that have an anabolic effect on muscle and could potentially counteract the formation of interfiber gaps induced by atrophy, which are known to be filled with fat. Several pharmacological substances influence the development, growth, and repair mechanisms of muscle, namely, anabolic steroids[11-20], growth hormones[21-24], β-2 agonists, heparan sulfate[25], xanthine derivatives[26], creatine[27], and vitamin D[28]. Of all of these substances, anabolic steroids seem best suited for clinical application. They enhance the synthesis of muscle proteins[14], induce hypertrophy of both type-I and II muscle fibers[19], and have an impact on satellite cell replication and activation[20] and on contractile strength[11]. Although their effect on treating established muscular alterations has been studied extensively, their effect on the prevention or reduction of deterioration of the muscle in a retracting musculotendinous unit is unknown.

The purpose of this study was to investigate whether anabolic steroids have a potential to lessen muscular changes caused by experimental musculotendinous retraction in a rabbit shoulder model.

Materials and Methods

Animal Model and Groups

This study was approved by the responsible investigational review board. A rabbit animal model was created: twenty New Zealand White rabbits with an average age of fifteen weeks and an average weight (and standard deviation) of 4.08 ± 0.42 kg underwent release of the supraspinatus tendon. Animals underwent preoxygenation through a face mask and received preoperative analgesia with intramuscular buprenorphine (10 μg per kilogram of body weight). Anesthesia was induced with medetomidine (5 μg/kg) and S-ketamine (7.5 mg/kg) intranasally before intubation was performed and inhalation anesthesia could be continued with isoflurane. After the right shoulder was shaved and disinfected, a skin incision of 5 cm was made parallel to the scapular spine and the supraspinatus tendon. The supraspinatus was visualized after dissection down to the deltoid muscle. Tendon release of the supraspinatus tendon was performed by osteotomy of the greater tuberosity. Intraoperative measurement of muscle strength as a function of different pretensions was performed in a standardized fashion both at the time of tendon release and at the time that the animal was killed. A force sensor (model 9203; Kistler, Winterthur, Switzerland) was connected to a fixator holding the sutures that grasped the tendon-bone chip complex. The fixator was stabilized by a firm connection to a sterilized rod with a threefold cusp that was positioned at the acromion. The suprascapular nerve was then stimulated with use of a needle electrode (Rochester Electro-Medical, Tampa, Florida) for supramaximal stimulation of the supraspinatus muscle with 20 mA and 40 Hz during 0.3 s. Stepwise release of the tension by 2 mm was allowed, starting at 10 N of passive pretension, and the force of the muscle was recorded before and during supramaximal stimulation during one contraction. The work was calculated by subtraction of the area under the curve of passive forces from the area under the curve of the maximal contractile forces over length.

Samples of the distal third of the supraspinatus muscle were harvested and fixed in formalin for further analysis before the tendon-bone chip complex was wrapped in a Penrose drain to prevent spontaneous healing, and the skin was closed. The musculotendinous unit was allowed to retract for six weeks without further intervention in seven animals (group I), with a weekly injection of nandrolone decanoate (50 ng/mL) partially locally into the supraspinatus muscle (0.4 mL locally and 0.8 mL into the quadriceps femoris muscle) in six animals (group II), or with total peripheral injection of nandrolone decanoate (0.6 mL each into the left and the right quadriceps muscle) in seven animals (group III) starting at the time of tendon release. In group II, only 0.4 mL of the substance was injected locally to diminish muscle changes caused by the oily carrier. An additional amount of 0.8 mL was injected systemically to achieve the same dosage as in group III with systemic application alone. Two animals from group III developed a postoperative infection at the site of the surgery and were killed four weeks after the initial surgery and excluded from the analysis. Postoperatively, the animals were allowed to walk freely, and they had a reoperation six weeks after the tenotomy to measure muscle work and to harvest biopsy specimens from both the operatively treated and the contralateral supraspinatus muscle before they were killed.

Imaging and Histological Evaluations

Computed tomographic (CT) measurements of retraction, atrophy, and fatty infiltration were performed both before and after tendon release with the rabbits in a lateral position. The measured retraction of the bone chip represented the amount of myotendinous retraction, the muscular cross-sectional area represented atrophy, and the density of the muscle, measured in Hounsfield units, represented fatty muscle infiltration and was determined with use of OsiriX software (version 3.6.1, 32 bit; http://www.osirix-viewer.com). The retraction of the tendon was measured by the distance between the bone chip and the site of the osteotomy at the greater tuberosity in the transverse plane. The osteotomy site was projected on the image where the bone chip was most clearly identifiable for measurement of the direct distance (Fig. 1). The cross-sectional area was measured at the transition from the middle to the distal third (determined in the corresponding transverse plane) of the supraspinatus muscle in the sagittal plane and is reported in total values and as a percent of the contralateral, control side. All imaging measurements were repeated, with an intervening period of two months, by the same observer (M.F.), who was blinded to the type of treatment applied and the first reading of the results. The mean value of two corresponding measurements was used for analysis. For imaging measurements made at the time the animals were killed, the intraobserver reliability assessed by the Pearson correlation was highest for the assessment of fatty infiltration ($r^2 = 0.81$), followed by measures of retraction ($r^2 = 0.75$), and was moderate for the determination of the cross-sectional area ($r^2 = 0.58$). After an animal was killed, the supraspinatus muscles of both shoulders were dissected and weighed. For histological and morphometric evaluation, samples were stained with hematoxylin-eosin. A fivefold magnification was achieved with the microscope to capture pictures as digital images (in tagged image file format [TIFF]) to document fiber diameter (Fig. 2) on hematoxylin-eosin-stained sections. In addition, the proportions of fat, muscle, fibrosis, and background were analyzed by means of

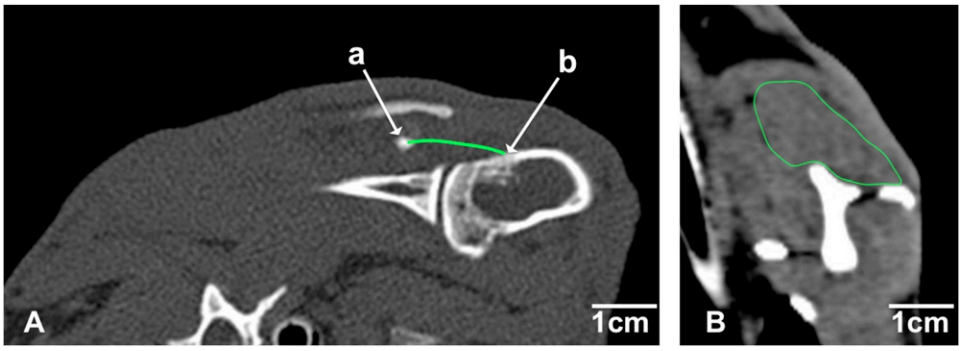

Fig. 1

Figs. 1-A and 1-B Computed tomographic (CT) scan of a rabbit shoulder in the lateral position, made six weeks after tendon release with use of osteotomy of the greater tuberosity with no additional treatment. **Fig. 1-A** The retraction of the bone chip was determined with use of CT in the axial plane by measurement of the distance between the bone chip (a) and the projection of the greater tuberosity (b) on the scan where the bone chip was clearly identifiable. **Fig. 1-B** The muscular cross-sectional area (outlined in green), as well as the density of the muscle tissue, was measured in the sagittal plane at the transition from the middle to the distal third of the supraspinatus muscle.

histomorphometry by a blinded observer, as described previously[5,10], by coloring four different phases with a software program (Adobe Photoshop 7; Adobe Systems, San Jose, California). The background, representing empty space on the histological sections, was subtracted before calculation of the proportional amounts of fat, muscle, and fibrosis. Fiber diameter was measured by defining a line that was perpendicular to the longitudinally cut muscle fibers that served as a guide for the measurement of ten consecutive and clearly identifiable fiber diameters, starting always at the lower right end of the image.

Statistical Analysis

For statistical analysis, the software GraphPad Prism (version 4; GraphPad Software, La Jolla, California) was used. Grouped data were tested for normal

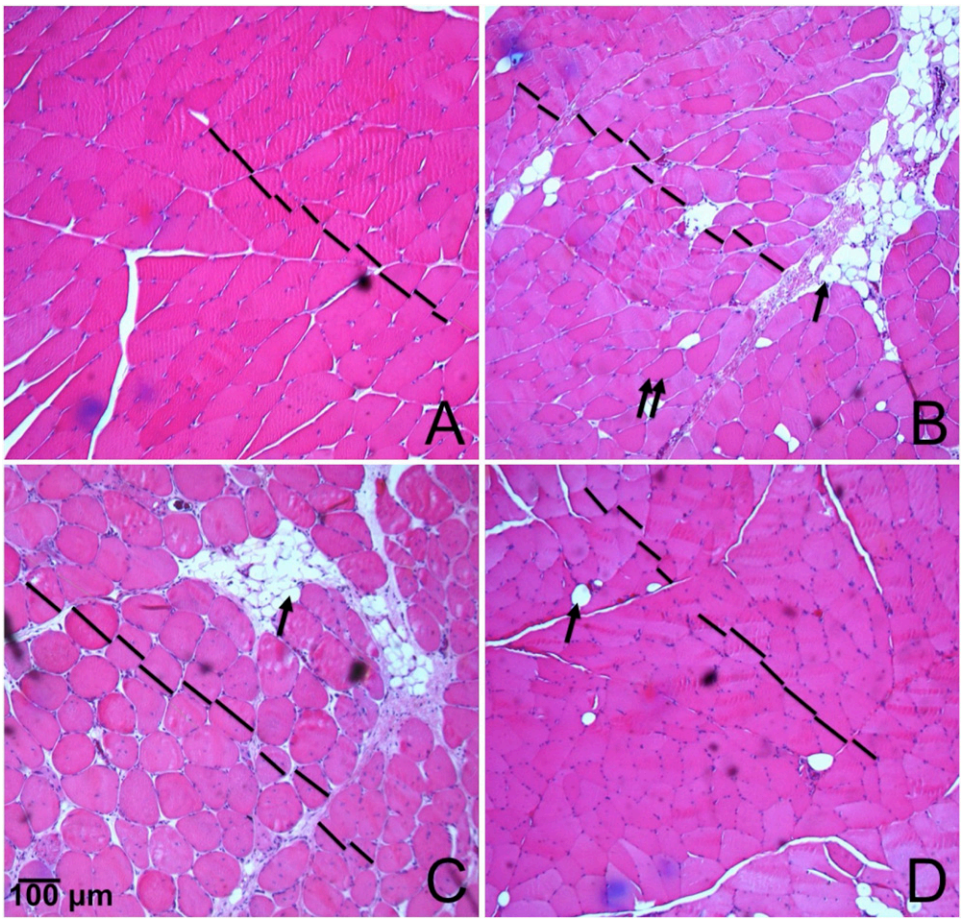

Fig. 2

Figs. 2-A through 2-D Histological cross sections of supraspinatus muscle (hematoxylin-eosin, ×5 in all four images). **Fig. 2-A** Normal supraspinatus muscle. **Fig. 2-B** Supraspinatus retraction and no treatment. **Fig. 2-C** Supraspinatus retraction with local and systemic nandrolone treatment. **Fig. 2-D** Supraspinatus retraction treated with systemic nandrolone. The diameter of muscle fiber (double arrows) was calculated as the mean of the (smallest) diameters of ten consecutive, clearly identifiable fibers. Interstitial infiltration with fat cells (arrow) was absent in the muscle of control animals before the intervention (Fig. 2-A) and was documented mostly in animals without steroid treatment (Fig. 2-B) and less so in animals with local and systemic nandrolone (Fig. 2-C) or those treated with systemic steroids (Fig. 2-D).

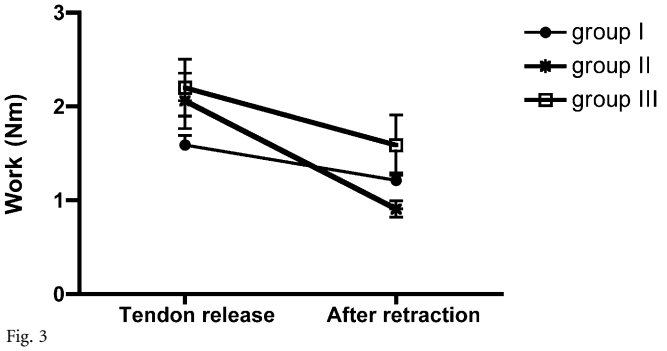

Fig. 3

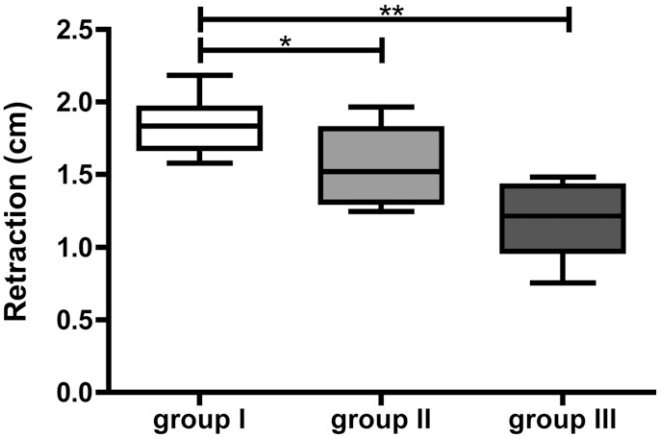

Fig. 4

Fig. 3 The work of the muscle decreased in group I (mean, 1.59 Nm [95% CI: 1.3, 1.88 Nm] to 1.2 Nm [95% CI: 0.99, 1.44 Nm]; p = 0.056) and group II (mean, 2.06 Nm [95% CI: 1.30, 2.82 Nm] to 0.9 Nm (95% CI: 0.68, 1.13 Nm]; p = 0.0528) but less in group III (mean, 2.2 Nm [95% CI: 1.36, 3.04 Nm] to 1.6 Nm [95% CI: 0.69, 2.48 Nm]; p = 0.23). The error bars indicate the standard error of the mean. **Fig. 4** The mean amount of retraction of the musculotendinous unit of the supraspinatus was highest in group I (1.8 cm; 95% CI: 1.64, 2.02 cm) followed by group II (1.5 cm; 95% CI: 1.29, 1.81 cm) and group III (1.2 cm; 95% CI: 0.86, 1.54 cm) and was significantly higher in group I than in group II (*p = 0.044) or III (**p = 0.001). Box plots are depicted with whiskers from minimum to maximum. The horizontal line in the middle of each box represents the median value, and the top and bottom borders of the box represent the 75th and the 25th percentile, respectively.

distribution with use of the Kolmogorov-Smirnov test before the use of either the Pearson correlation for Gaussian population or the Spearman correlation for nonparametric data. Intragroup comparison was performed with use of the two-tailed paired Student t test or Wilcoxon matched pairs test for normally distributed and not normally distributed data, respectively. Intergroup comparison was performed with use of the two-tailed paired Student t test or the Mann-Whitney test for normally distributed and not normally distributed data, respectively, and for both comparisons of different groups or intersample comparisons of the treated and the contralateral side. Values are reported as the mean and the standard deviation or as the range (minimum to maximum), when applicable. The level of significance was set at $p < 0.05$.

Source of Funding

The experiments and data analysis within this study were funded by the Balgrist Stiftung.

Results

Work of the Muscle

The work of the muscle during one standardized supramaximal stimulation decreased in all groups. The decrease was from 1.59 Nm (95% confidence interval [95% CI]: 1.3, 1.88 Nm) to 1.2 Nm (95% CI: 0.99, 1.44 Nm) (p = 0.056) in group I, from 2.06 Nm (95% CI: 1.30, 2.82 Nm) to 0.9 Nm (95% CI: 0.68, 1.13 Nm) (p = 0.0528) in group II, and from 2.2 Nm (95% CI: 1.36, 3.04 Nm) to 1.6 Nm (95% CI: 0.69, 2.48 Nm) (p = 0.23) in group III (Fig. 3).

Imaging Measurements

The amount of retraction was highest for group I (1.8 cm; 95% CI: 1.64, 2.02 cm), followed by group II (1.5 cm; 95% CI: 1.29, 1.81 cm) and group III (1.2 cm; 95% CI: 0.86, 1.54 cm) (Fig. 4), and was significantly higher in group I than in group II (p = 0.044) or group III (p = 0.001). There was a significant decrease of Hounsfield units (H) as an indicator of fatty infiltration on the CT images, from 62 H (95% CI: 60.1, 63.2 H) to 43 H (95% CI: 34.5, 51.7 H) in the untreated animals (group I; p = 0.002), a moderate decrease in group II (57 H [95% CI: 53.4, 61.0 H] to 49 H [95% CI: 41.4, 57.5 H]; p = 0.089), and no apparent change in group III (67 H [95% CI: 59.1, 74.3 H] to 65 H [95% CI: 58.2, 72.2 H]; p = 0.76) (Fig. 5). The cross-sectional area set in relation to the contralateral side, measured on sagittal CT images, decreased from 107% (95% CI: 96%, 117%) to 82% (95% CI:

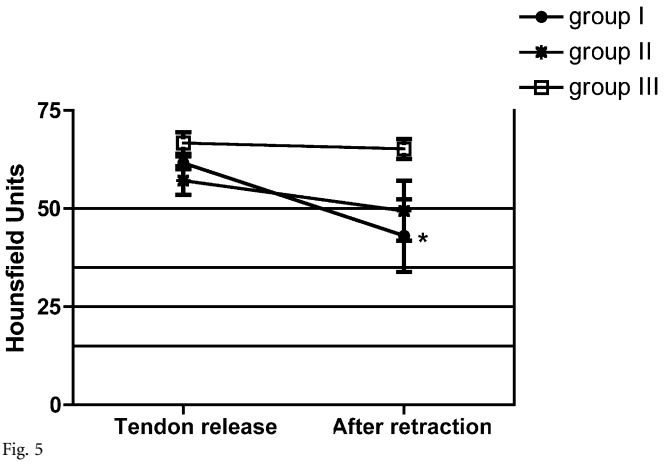

Fig. 5

The mean Hounsfield units (H), as an indicator for fatty infiltration in the CT image, decreased significantly from 62 H (95% CI: 60.1, 63.2 H) to 43 H (95% CI: 34.5, 51.7 H) in the untreated animals (group I; p = 0.002*) and remained nearly similar with 57 H (95% CI: 53.4, 61 H) to 49 H (95% CI: 41.4, 57.5 H) (p = 0.089) in group II and 67 H (95% CI: 59.1, 74.3 H) to 65 H (95% CI: 58.2, 72.2 H) (p = 0.76) in group III. The error bars represent the standard error of the mean.

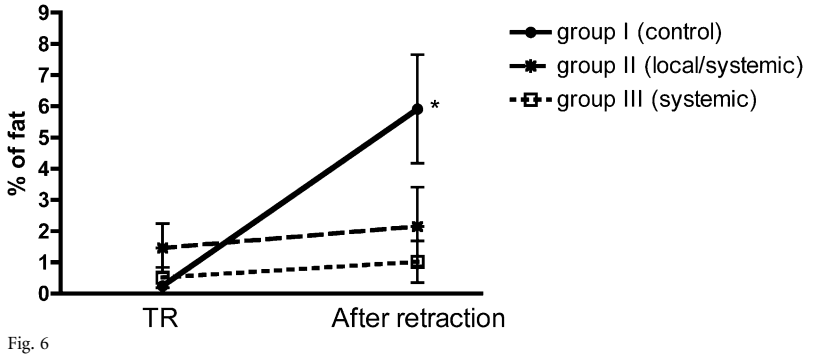

Fig. 6

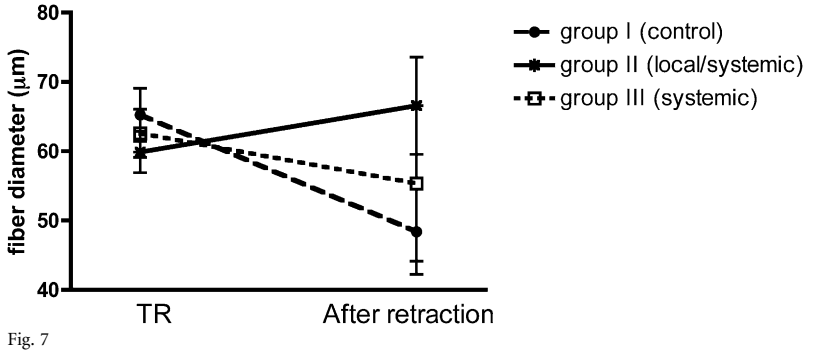

Fig. 7

Fig. 6 No significant histological fatty infiltration was noted in the groups with systemic administration of nandrolone decanoate after tendon release (TR) (mean, 1.5% [range, 0% to 3.9%] to 2.2% [range, 0% to 8%] in group II and 0.5% [range, 0% to 1.6%] to 1.0% [range, 0% to 3.4%] in group III), whereas fatty infiltration was documented in the untreated animals in group I (mean, 0.3% [range, 0% to 1.1%] to 5.9% [range, 0% to 14.1%]; p = 0.031*). The error bars represent the standard error of the mean. **Fig. 7** Muscle fiber diameter decreased most after tendon release in group I (mean, 65 μm [95% CI: 56; 75 μm] to 48 μm [95% CI: 33, 64 μm]; p = 0.063) and remained similar in the treated groups II (mean, 60 μm [95% CI: 52, 68 μm] to 67 μm (95% CI: 48, 85 μm]) and III (mean, 63 μm [95% CI: 53, 72 μm] to 55 μm [95% CI: 24, 86 μm]; p = 0.640). The error bars indicate the standard error of the mean.

72%, 92%) in group I (p = 0.005), 97% (95% CI: 26%, 148%) to 73% (95% CI: 61%, 84%) in group II (p = 0.317), and 113% (95% CI: 98%, 130%) to 79% (95% CI: 59%, 99%) in group III (p = 0.0131). However, the total values of the cross-sectional area did not change significantly in group III with systematic application of nandrolone (2.16 cm^2 [95% CI: 1.75, 2.58 cm^2] to 1.90 cm^2 [95% CI: 1.72, 2.08 cm^2]; p = 0.149), whereas the values decreased significantly in group I (1.99 cm^2 [95% CI: 1.65, 2.33 cm^2] to 1.55 cm^2 [95% CI: 1.34, 1.76 cm^2]; p = 0.013) and group II (2.27 cm^2 [95% CI: 1.98, 2.56 cm^2] to 1.72 m^2 [95% CI: 1.34, 2.08 cm^2]; p = 0.030). The decrease in the total value of the cross-sectional area was significantly higher in the untreated animals (group I) than in the animals that had systemic application of nandrolone (group III) (p = 0.010).

Gross Anatomy and Histological Findings

At the time that the animals were killed, the weight of the operatively treated supraspinatus muscles trended from lower to higher values for group I (7.4 g; 95% CI: 5.9, 8.9 g), followed by group II (8.7 g; 95% CI: 6.4, 11 g) and then group III (9.4 g; 95% CI: 8.1, 10.7 g); the differences were not significant (p = 0.29 for group I versus II and p = 0.073 for group I versus III). According to histomorphometric measures, muscle tissue diminished the most in group I but was apparently preserved in group I (see Appendix). The amount of fibrous tissue at the time of killing was the similar to the baseline amount at the time of tenotomy in group II, but it was higher than baseline in groups I and III after six weeks of retraction (see Appendix). No significant fatty infiltration occurred in the pharmacologically treated animals (groups II and III), whereas significant fatty infiltration was noted after chronic retraction in the untreated animals (group I) (see Appendix and Fig. 6). The diameter of muscle fiber trended toward a decrease in group I (65 μm [95% CI: 56, 75 μm] to 48 μm [95% CI: 33, 64 μm]; p = 0.063) and remained similar in the treated groups II (60 μm [95% CI: 52, 68 μm] to 67 μm (95% CI: 48, 85 μm]; p = 0.498) and III (63 μm [95% CI: 53, 72 μm] to 55 μm (95% CI: 24, 86 μm]; p = 0.640) (Fig. 7).

Discussion

The structural and functional alterations of the musculotendinous unit as a consequence of chronic tendon tears are considered irreversible on direct tendon repair and have been shown to be partly reversible with continuous relengthening of the retracted myotendinous unit[10]. It is desirable to inhibit the development of these changes in the first place. If a surgical repair cannot be performed shortly after a supraspinatus tear, a pharmacological approach to inhibit muscle degeneration could be valuable. We documented inhibition of fatty infiltration and partial preservation of muscle function by administration of nandrolone decanoate during musculotendinous retraction in a rabbit rotator cuff tear model. These experimental observations suggest a new approach with potential for preventing tendon-tear-induced muscle deterioration.

This study has some limitations. First, this is an animal study and translation of these findings to the human should be made with caution. The rabbit rotator cuff model is well accepted for investigation of pathologic conditions of muscle because it reproduces the key structural findings for muscle deterioration seen in humans and sheep after detachment of its tendon[29-32]. This study focused exclusively on the muscle tissue and did not investigate the tendon, primarily because

the available amount of tendon tissue was insufficient for a biopsy-based analysis. The rat model has been proposed for studies of pathological conditions of the supraspinatus tendon on the basis of the similarity of the subacromial anatomy to the human shoulder[33]. So far, investigators have failed to quantitatively satisfactorily reproduce the characteristic muscular changes seen in humans and sheep with use of the rat model[34,35]. The sheep model is well established for investigations of muscular and tendinous rotator cuff abnormality[5,10,36-39]. Although investigations in which technical feasibility (e.g., implantation of a device to continuously relengthen retracted myotendinous units[10]) favors large-animal models, we found the current smaller-animal model suitable to answer the research questions at hand while reducing the cost and ethical burden. Although the fatty infiltration observed in the rabbit rotator cuff model is multiple times lower than levels seen in the human[40], the model provided sufficient sensitivity to assess the effectiveness of the pharmacological intervention.

The optimal time allowed for retraction and development of muscular changes in the rabbit rotator cuff model is controversial; Björkenheim documented peak alteration after six weeks of retraction[32], and other authors have suggested the possibility for further progression[31,41]. It was not the purpose of this study to investigate the evolution of muscular changes over time, but to study the animals before and after a substantial muscular alteration had been induced by the release of the supraspinatus tendon and consequent musculotendinous retraction. Significant deterioration of the detached muscle was observed within six weeks of retraction in the untreated group, and substantial differences between the control and test groups were identified. We believe that proof of principle was sufficiently established and that the original hypothesis was confirmed.

Second, potentially detrimental side effects of the applied anabolic steroid were not investigated. Two animals with systemic application of nandrolone decanoate developed wound infections, and we do not know whether the steroid was causative. Further, translation of our findings to humans regarding potential beneficial effects of nandrolone decanoate needs further research. The effect of anabolic steroids on striated muscle is well known: application causes increased lean body mass and muscle protein synthesis in man[11,15,17,18,42,43]. Nandrolone decanoate, a derivative of testosterone, is recommended and is used to counteract catabolic processes in patients with postmenopausal osteoporosis[44,45], sequelae of kidney disease[46,47], and muscle wasting in human immunodeficiency virus[48]. Although we believe that nandrolone decanoate will produce a similarly beneficial effect in humans as observed in our animal model, further research is needed to determine optimal dose-effect relationships and delivery methods. In our study, the dose of nandrolone decanoate was supramaximal and the substance was delivered in an oily solution. Although we expected an increased amount of fibrosis in group II because of a local inflammatory effect of the oily adjuvant[49], the opposite effect was observed. It remains unknown whether the local administration of nandrolone decanoate had overwhelmed the inflammatory effect of its carrier and/or if other carriers might be more effective.

Third, all animals were allowed to walk freely and we did not document the activity levels of the animals. We do not know whether administration of the anabolic steroid may have increased the activity level of the animals and therefore acted as a potentially confounding factor in the relationship between pharmacological intervention and effects on muscle tissue. However, since the cage size was limited and equally sized for all animals, and the musculotendinous unit was detached from its insertion in all animals, it seems unlikely that the muscle could have been preferentially trained in any group of animals.

The observed prevention of fatty muscle infiltration, and reduction of fiber atrophy and fibrosis, stands in contrast to the other studies that did not use any pharmacological stimulus for the retracting muscle[31,32,41] and adds a new dimension to the understanding of fatty muscle infiltration. Functionally, the effect was less evident, perhaps because of technical difficulties, consisting of variability in the amount of preparation of the retracted tendon-bone chip complex performed to release the variable amount of fixation to the surrounding tissue.

Although these experimental results in rabbits cannot and should not be directly translated into clinical practice, the first success of this prophylactic pharmacological concept for partial prevention of structural alterations that are currently accepted as unavoidable and irreversible opens new research potential. Other growth hormones and myogenic stimulators should be tested for their preventive potential, and nandrolone decanoate should be tested further, particularly as optimal dosage has not been addressed. Further, potential adverse effects on the tendinous tissue as well as systemic adverse effects of anabolic steroids should be considered.

Appendix

eA A table showing muscle, fat, and fibrotic tissue as a percentage of total tissue according to histomorphometric measurement at tenotomy and after six weeks of chronic musculotendinous retraction is available with the online version of this article as a data supplement at jbjs.org. ■

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